Child Neurology: Migraine with aura in children

Amy A. Gelfand, MD
Heather J. Fullerton, MD, MAS
Peter J. Goadsby, MD, PhD

Address correspondence and reprint requests to Dr. Amy A. Gelfand, UCSF Department of Neurology, Box 0114, 505 Parnassus Ave, M-798, San Francisco, CA 94143-0114
GelfandA@neuropeds.ucsf.edu

ABSTRACT

The differential diagnosis for an acute hemiparesis in a child includes stroke, Todd paralysis, and hemiplegic migraine. In the context of an illustrative case, this review highlights the differences in clinical presentation among these entities and an approach to the diagnostic workup. Migraine with aura in children is reviewed, including migraine equivalents such as abdominal migraine and the particular presentation of hemiplegic migraine. An approach to the prophylactic and acute treatment for children with migraine with aura is offered. *Neurology*® 2010;75:e16–e19

CASE: PART 1 A 14-year-old boy with Crohn disease was admitted for a presumed flare. On the second hospital day, his abdominal pain acutely increased. Shortly thereafter, he experienced tingling starting in his shoulder and spreading over his left hemibody over 10 seconds. This was accompanied by 7/10 pounding left-sided head pain. Several minutes later, the tingling gave way to diminished sensation and weakness on the left. These symptoms persisted into the next morning, at which time a neurologic consultation was requested.

Now 20 hours into the attack, he had 5/10 pounding head pain. Neurologic examination revealed a left hemiparesis in a pyramidal distribution, with face and arm affected more than leg. Sensation was also diminished over the left face and hemibody. Reflexes were normal and there was no neglect. Complete blood count, electrolytes, erythrocyte sedimentation rate, liver function tests, lactate, amylase, and lipase were normal.

Differential diagnosis. The differential diagnosis for acute onset hemiparesis in a child includes stroke, Todd paralysis, and migraine with aura, specifically hemiplegic migraine. Demyelinating disease, brain tumor, and metabolic disturbances such as hypoglycemia or hypocalcemia should also be considered.

Patients with inflammatory bowel disease are often hypercoagulable, increasing their risk of ischemic stroke.[1] Positive symptoms such as tingling are more suggestive of migraine, while stroke is classically associated with negative symptoms. However, children with ischemic and hemorrhagic stroke can complain of tingling paresthesias.

In this case, there was no witnessed seizure activity or change in mental status. Postictal paralysis is also usually not so prolonged. In a study of adults in an epilepsy monitoring unit, Todd paresis resolved within 22 minutes,[2] though in one pediatric case report it lasted 24 hours.[3]

Migraine with prolonged aura would be a diagnosis of exclusion given this was his first presentation, and that children often complain of headache at the ictus of both hemorrhagic and ischemic strokes.[4]

Recommended workup. Additional history important to elicit includes whether there is a family history of epilepsy, migraine, or hypercoagulability. The presence of migraine markers, such as motion sickness and ice cream headache (throbbing head pain when eating something cold),[5] should also be sought.

Given that migraine with prolonged aura is difficult to differentiate from acute stroke, on first presentation these patients should be imaged with MRI and intracranial magnetic resonance angiography to rule out ischemia. Imaging also rules out vasculitis or moyamoya disease, which may present with headache with a migrainous phenotype, probably as a comorbid activation of the patient's underlying tendency to migraine.

CASE: PART 2 MRI with diffusion-weighted imaging, which is highly sensitive for acute infarction, was normal. Magnetic resonance angiography and venography were also normal. By 26 hours after symptom

From the Division of Child Neurology (A.A.G., H.J.F.), Neurovascular Division (H.J.F.), and Headache Group, Department of Neurology (P.J.G.), University of California, San Francisco, San Francisco, CA.
Disclosure: Author disclosures are provided at the end of the article.

onset, the patient's weakness began improving, and by the next morning his neurologic examination was normal.

Further history revealed that the patient experienced monthly headaches which were unilateral, throbbing, and partially relieved by acetaminophen. His mother and older sister had frequent severe headaches, though neither experienced aura. The patient had not experienced aura symptoms with his previous headaches or episodes of abdominal pain.

He did experience motion sickness and frequent abdominal pain and vomiting as a young child. He did not get ice cream headache.

Review of the patient's records revealed that the diagnosis of Crohn disease was purely clinical—he had never had biopsy-proven pathology. He had never experienced bloody or mucous-covered stools, extraintestinal manifestations of Crohn disease, or highly elevated inflammatory makers. His abdominal pain came on more with stress and with nitrite-containing foods, both known migraine triggers. Often the episodes of abdominal pain lasted only 1–2 hours.

A repeat endoscopy and intestinal biopsies were negative for evidence of Crohn disease, raising significant doubts about this diagnosis. His gastrointestinal symptoms were considered to most likely be due to abdominal migraines.

MIGRAINE WITH AURA IN CHILDREN Migraine is common in children.[6] The prevalence is 3% in children aged 3–7 years, 4%–11% in those 7–11 years, and 8%–23% in teenagers.[6] One quarter of patients with migraine experience aura.[7] Aura is thought to be based on cortical spreading depression; a wave of depolarization followed by hyperpolarization spreads across the cortex, precipitating neurologic dysfunction.[8,9] Prognostically, 50%–60% of adolescents with migraine with aura are still symptomatic at 5- to 7-year follow-up.[8]

In migraine with typical aura, visual, sensory, or dysphasic symptoms develop over 5–20 minutes, and resolve within 60 minutes. Headache typically occurs with the aura, or follows within 60 minutes.[10] The headache may be ipsilateral or contralateral to the aura symptoms, usually contralateral.[11] Visual auras are most common, followed by sensory, then language.[12] Motor aura is least common and is a defining feature of hemiplegic migraine.[13]

This patient's hemisensory tingling was most likely a typical aura, even though it came on quickly. The slow, spreading quality of migraine aura is often helpful in distinguishing it from ischemic deficits, which tend to be maximal at onset.[12] Neurologic deficits from aura usually resolve within 20–60 minutes, though this is also often the case in transient ischemic attacks. In migraine aura, positive symptoms such as tingling are often followed minutes later by negative symptoms,[12] as they were in this case when the tingling gave way to diminished sensation. A migratory pattern, or so-called Jacksonian march,[14] can also be seen in seizure.

Migraine with prolonged aura. Aura in migraine is considered prolonged if it lasts more than 1 hour but less than 7 days,[15] with longer aura termed persistent aura.[10] Most patients experience prolonged aura in only a minority of attacks, often experiencing typical length aura with other attacks.[16]

Adult patients with migraine with aura are at greater stroke risk than controls, although the absolute risk remains small, estimated in one study at 12.4 ischemic strokes per 10,000 women per year.[17-19] It is not known whether prolonged aura carries a greater risk for vascular events than typical aura.

Hemiplegic migraine. Hemiplegic migraine can be familial[20] or sporadic.[21] The familial form may be due to mutations in voltage-gated channels *CACNA1A*[22] and *SCN1A*[23] or the Na^+/K^+ pump *ATP1A2* gene.[24] The etiology of the sporadic form, which this patient had, is less clear, although some patients have mutations in the same genes.[25]

The motor aura of hemiplegic migraine is unique. There is no biphasic symptom progression, specifically no jerking before the onset of weakness.[12] While most attacks come on over minutes, 7% of patients experience onset of weakness in under 1 minute,[26] as this patient did. The weakness is twice as likely to affect the arm as the leg.[26] Duration can be hours to days, though most still resolve within an hour.[26,27] Most patients also experience typical aura symptoms during an attack, usually sensory, as this patient did.[26] The hemiplegia is almost always accompanied by head pain, unlike other auras (e.g., visual), which can occur without headache.[27] The pathophysiology of motor aura is now being explored with mouse models as the genes have been identified.[28] Some have hypothesized that the aura in hemiplegic migraine is from vasospasm, not cortical spreading depression. However, there is no evidence for this or for increased stroke risk over other migraines with aura.[29]

Abdominal migraine. Abdominal migraine is one of several childhood migraine equivalents. These syndromes are thought to be developmental manifestations of genes that in adulthood will be expressed as migraine headache. An example of this potential is that benign torticollis of childhood can be linked to the familial hemiplegic migraine gene *CACNA1A*.[30] Children with migraine equivalents make up an estimated 10% of all migraineurs referred to pediatric

neurology clinics.[6] Three migraine equivalent syndromes are recognized in International Classification of Headache Disorders–II: cyclical vomiting, abdominal migraine, and benign paroxysmal vertigo of childhood.[8] Several others are proposed: benign paroxysmal torticollis of infancy,[30,31] acephalgic migraine,[32] and acute confusional migraine.[6,33]

Abdominal migraine presents in school-aged children as periumbilical or midline dull abdominal pain that lasts 1 to 72 hours.[8] There may be associated anorexia, nausea, vomiting, or pallor.[6,8] There is usually a family history of migraine, and about 70% of children also have typical migraines, although it may be several years before these emerge.[6]

TREATMENT OF MIGRAINE WITH AURA IN CHILDREN

Prophylaxis. The decision of when prophylaxis is indicated can only be made in conjunction with the family or caregivers. Even relatively infrequent migraines may merit daily treatment if they are frightening to the child, or likely to trigger repeated unnecessary imaging studies, such as in hemiplegic migraine. In fact, the US Headache Consortium recommends prophylactic therapy for those whose migraines are accompanied by hemiplegia or prolonged aura.[34] Preventive migraine therapies in children and adolescents were recently reviewed[8]; this discussion focuses specifically on treatment of migraine with aura.

There is no proven treatment for migraine with aura. In a survey of adult headache specialists, 55% thought verapamil was most effective, while 18% preferred valproate.[16] Flunarizine is widely used in the United Kingdom and particularly effective in children with hemiplegic migraine.[35] Verapamil may also be effective for hemiplegic migraine,[34,36] lamotrigine for aura in general, and divalproex for persistent aura.[34,37] One open-label study with ketamine suggests that the development of suitable agents with actions at excitatory glutamate receptors may be one way forward.[38,39] Many headache specialists avoid beta-blockers in patients with prolonged aura out of concern that they may limit compensatory vasodilation, although this is more a theoretical concern.[16]

The best prophylactic therapy for migraine with aura remains to be established, and on the individual level often requires trial and error. Calcium-channel blockers are a reasonable first choice. Given the often cyclical nature of migraine, the duration of prophylactic therapy need not be interminable. One approach is to treat for the duration of the school year and wean over the summer.[8]

Acute therapies. With present knowledge, acute aura itself is not treatable. Treatment should therefore focus on the head pain. Acetaminophen and nonsteroidal anti-inflammatory drugs are first-line agents.[8] Almotriptan is approved by the Food and Drug Administration for acute migraine therapy in adolescents.[40] Several other triptans have been studied in adolescents and children and used off-label, most notably nasal spray sumatriptan.[8] In case reports, IV verapamil seems effective for acute hemiplegic migraine.[36] Triptans are contraindicated in hemiplegic migraine because it was wrongly considered when they were developed that vasospasm was an important part of migraine aura, and there are thus insufficient systematic data upon which to base any other recommendation.

CASE CONCLUSION On follow-up 7 weeks later, the patient reported no further episodes of abdominal pain or headache. Given the current infrequency of his symptoms, he and his parents did not desire prophylaxis. The decision was made to treat acute episodes with naproxen. If his migraines become more frequent, he will start verapamil.

DISCLOSURE

Dr. Gelfand serves on the Resident & Fellow Editorial Team for *Neurology®*. Dr. Fullerton serves on the DSMB for Berlin Heart; serves on the editorial board of *Pediatric Neurology*; receives research support from the NIH (NINDS R01 NS062820 A2 [contact PI] and NINDS K02 NS053883 [PI]) and the American Heart Association; and has provided expert testimony in legal proceedings regarding children with stroke. Dr. Goadsby has served as a consultant for or served on a scientific advisory board for Advanced Bionics, Allergan, Inc., Almirall, Amgen, ATI, AstraZeneca, Belgian Research Council, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific, CoLucid Pharmaceuticals, Coherex Medical, Inc., Eli Lilly & Company, Fidelity Foundation, GlaxoSmithKline, Johnson & Johnson, Kalypsys Inc., Medtronic, Inc., MAP Pharmaceuticals, Inc., Migraine Research Foundation, Migraine Trust, Minster Pharmaceuticals plc, Medical Research Council–UK, Merck & Co., Inc., the NIH/NINDS (consultant), Netherlands Research Council, Neuralieve, NeurAxon Inc., NeuroTherapeutics Pharma, Organisation for Understanding Cluster Headache–UK and US, and Pfizer Inc.; serves on the editorial board of *Cephalalgia*; receives royalties from the publication of *Mechanism and Management of Headache, 7th ed.* (Elsevier, 2005); and has received research support from GlaxoSmithKline, Neuralieve, Merck & Co., Inc., Johnson & Johnson, and MAP Pharmaceuticals, Inc.

Received December 21, 2009. Accepted in final form April 6, 2010.

REFERENCES

1. Mori K, Watanabe H, Hiwatashi N, Sugai K, Goto Y. Studies on blood coagulation in ulcerative colitis and Crohn's disease. Tohoku J Exp Med 1980;132:93–101.
2. Gallmetzer P, Leutmezer F, Serles W, Assem-Hilger E, Spatt J, Baumgartner C. Postictal paresis in focal epilepsies: incidence, duration, and causes: a video-EEG monitoring study. Neurology 2004;62:2160–2164.
3. Kimura M, Sejima H, Ozasa H, Yamaguchi S. Technetium-99m-HMPAO SPECT in patients with hemiconvulsions followed by Todd's paralysis. Pediatr Radiol 1998;28:92–94.
4. Giroud M, Lemesle M, Madinier G, Manceau E, Osseby GV, Dumas R. Stroke in children under 16 years of age: clinical and etiological difference with adults. Acta Neurol Scand 1997;96:401–406.

5. Selekler HM, Erdogan MS, Budak F. Prevalence and clinical characteristics of an experimental model of 'ice-cream headache' in migraine and episodic tension-type headache patients. Cephalalgia 2004;24:293–297.
6. Al-Twaijri WA, Shevell MI. Pediatric migraine equivalents: occurrence and clinical features in practice. Pediatr Neurol 2002;26:365–368.
7. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 1992; 12:221–228; discussion 186.
8. Lewis DW. Pediatric migraine. Neurol Clin 2009;27:481–501.
9. Lauritzen M. Pathophysiology of the migraine aura: the spreading depression theory. Brain 1994;117:199–210.
10. The International Classification of Headache Disorders, 2nd edition. Cephalalgia 2004;24(suppl 1):9–160.
11. Lance JW, Goadsby PJ. Mechanism and Management of Headache, 6th ed. Boston: Butterworth Heinemann; 1998.
12. Foroozan R, Cutrer FM. Transient neurologic dysfunction in migraine. Neurol Clin 2009;27:361–378.
13. Young W, Silberstein S. Migraine: spectrum of symptoms and diagnosis. Continuum Headache 2006;12:67–86.
14. Jackson JH. Notes on the physiology and pathology of the nervous system. Med Times Gaz 1868;ii:696.
15. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 1988;8(suppl 7):1–96.
16. Evans RW, Lipton RB. Topics in migraine management: a survey of headache specialists highlights some controversies. Neurol Clin 2001;19:1–21.
17. Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population-based study. Neurology 2010;74:628–635.
18. Kurth T. Migraine and ischaemic vascular events. Cephalalgia 2007;27:965–975.
19. Kurth T, Slomke MA, Kase CS, et al. Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 2005;64:1020–1026.
20. Goadsby PJ. Hemiplegic migraine-a cerebral ionopathy. In: Squire LR, ed. New Encyclopedia of Neuroscience. Oxford: Academic Press; 2009:1073–1080.
21. Thomsen LL, Ostergaard E, Romer SF, et al. Sporadic hemiplegic migraine is an aetiologically heterogeneous disorder. Cephalalgia 2003;23:921–928.
22. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene *CACNL1A4*. Cell 1996;87:543–552.
23. Dichgans M, Freilinger T, Eckstein G, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet 2005;366:371–377.
24. De Fusco M, Marconi R, Silvestri L, et al. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 2003;33:192–196.
25. Thomsen LL, Kirchmann M, Bjornsson A, et al. The genetic spectrum of a population-based sample of familial hemiplegic migraine. Brain 2007;130:346–356.
26. Thomsen LL, Ostergaard E, Olesen J, Russell MB. Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. Neurology 2003;60:595–601.
27. Bhatia R, Desai S, Tripathi M, et al. Sporadic hemiplegic migraine: report of a case with clinical and radiological features. J Headache Pain 2008;9:385–388.
28. van den Maagdenberg AM, Pietrobon D, Pizzorusso T, et al. A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 2004;41:701–710.
29. Klapper J, Mathew N, Nett R. Triptans in the treatment of basilar migraine and migraine with prolonged aura. Headache 2001;41:981–984.
30. Giffin NJ, Benton S, Goadsby PJ. Benign paroxysmal torticollis of infancy: four new cases and linkage to *CACNA1A* mutation. Dev Med Child Neurol 2002;44: 490–493.
31. Rosman NP, Douglass LM, Sharif UM, Paolini J. The neurology of benign paroxysmal torticollis of infancy: report of 10 new cases and review of the literature. J Child Neurol 2009;24:155–160.
32. Shevell MI. Familial acephalgic migraines. Neurology 1997;48:776–777.
33. Khatri R, Hershey AD, Wong B. Prochlorperazine–treatment for acute confusional migraine. Headache 2009;49: 477–480.
34. Wheeler SD. Phenotype-driven preventive strategies for migraine and other headaches. Neurologist 2009;15: 59–70.
35. Basheer A, Goadsby PJ, Prabhakar P. Flunarizine for paediatric headache: a ten year review. Cephalalgia (in press 2010).
36. Yu W, Horowitz SH. Treatment of sporadic hemiplegic migraine with calcium-channel blocker verapamil. Neurology 2003;60:120–121.
37. Rothrock JF. Successful treatment of persistent migraine aura with divalproex sodium. Neurology 1997;48:261–262.
38. Kaube H, Herzog J, Kaufer T, Dichgans M, Diener HC. Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. Neurology 2000; 55:139–141.
39. Andreou AP, Goadsby PJ. Therapeutic potential of novel glutamate receptor antagonists in migraine. Expert Opin Investig Drugs 2009;18:789–803.
40. Linder SL, Mathew NT, Cady RK, Finlayson G, Ishkanian G, Lewis DW. Efficacy and tolerability of almotriptan in adolescents: a randomized, double-blind, placebo-controlled trial. Headache 2008;48:1326–1336.